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⑤4 4—ヒドロキシ—6—ピリジルピリミジン誘導体の製造法

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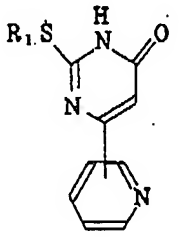
発明の詳細な説明

本発明は新規な4—ヒドロキシ—6—ピリジルピリミジン誘導体、特に一般式



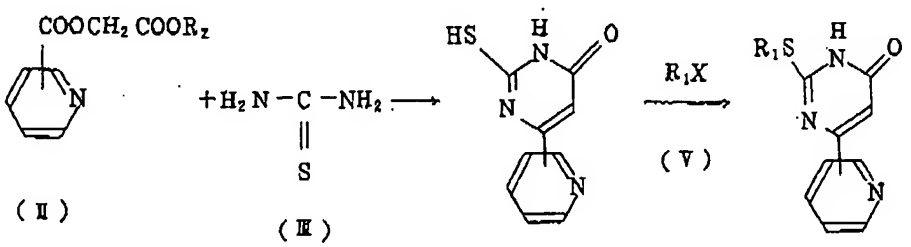
(I)

(式中、R_1は低級アルキル基を示す)で表わされる4—ヒドロキシ—6—ピリジルピリミジン誘導体(I)の製造法に関するものである。

而して、本発明方法は優れた抗炎症作用を有する医薬品として有用な化合物を製造するための重要な中間体を提供せんとするにある。

従来、ピリミジン誘導体のある種の化合物が抗炎症作用を有することが知られている。そこで本願発明者らはピリミジン誘導体の一連の化合物を合成し、その抗炎症作用を検討したところ、ピリミジン骨格の6位にピリジル基を有し、2位および4位にアミノ基、アルコキシ基またはアルキルチオ基を有する化合物が優れた抗炎症作用を有することを知見するとともに医薬品として有用なこれらの化合物を製造するための重要な中間体(I)を得ることに成功し本発明に到達した。

本発明方法は次の反応式によつて示される。



(II)　(III)　(IV)　(V)　(I)

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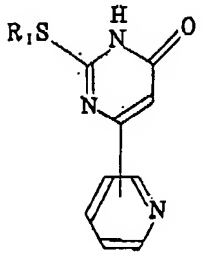
で表わされる化合物に一般式

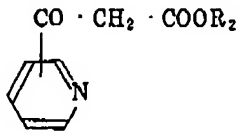
$$R_1 - X$$

（式中 R_1 は低級アルキル基を、Xはハロゲン原子を示す）で表わされる化合物を反応せしめることを特徴とする、一般式



（式中、R_1 は前記の意味を有する）で表わされる4－ヒドロキシ－6－ピリジル－ピリミジン誘導体の製造法。

2　一般式



（式中、R_2 は低級アルキル基を示す）で表わされる化合物にチオ尿素を反応せしめて式

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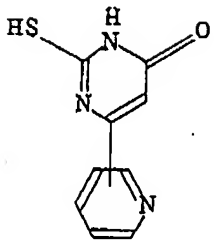
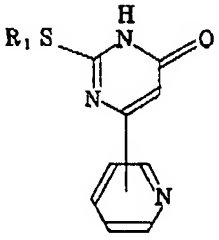


で表わされる化合物となし、次いでこれに一般式

$$R_1 - X$$

（式中R_1 は低級アルキル基を、Xはハロゲン原子を示す）で表わされる化合物を反応せしめることを特徴とする一般式



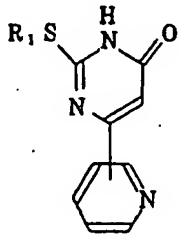
（式中、R_1 は前記の意味を有する）で表わされる4－ヒドロキシ－6－ピリジル－ピリミジン誘導体の製法。

Patent Publication of examined application (Kokoku) No.49-35632
Publication Date September 25, 1974

Title of the invention: Method of preparing 4-Hydroxy-6-pyridylpyrimidine derivatives
Application number: Showa 45-127612
Application date: December 28, 1970
Inventors: Tani, Hideo
Nakamura, Koji
Mori, Yasuhiro
Yokoo, Nobuo
Kyotani, Yoshinori
Wada, Yasushi
Applicant: Kowa company

Detailed Explanation of Invention

The present invention relates to a method of preparing novel 4-hydroxy-6-pyridylpyrimidine derivatives, particularly, 4-hydroxy-6-pyridylpyrimidine derivative (I) represented by the general formula:



(I)

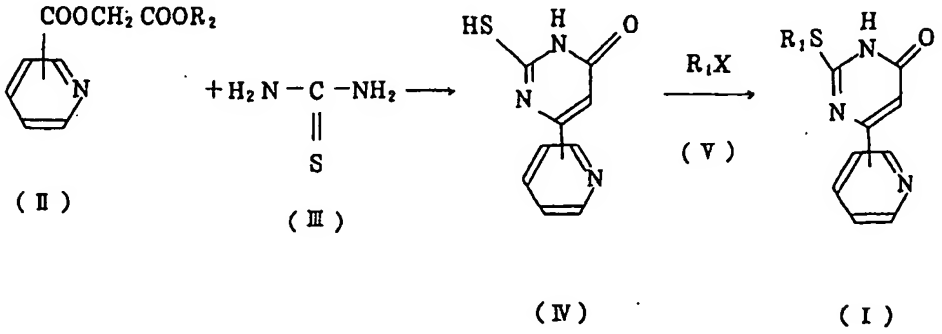
wherein R^1 represents a lower alkyl group.

Method of the present invention is thus to provide a key intermediate for producing a compound useful as a medicament having excellent anti-inflammatory activity.

It is conventionally known that a certain class of pyrimidine derivatives has anti-inflammatory activity. Therefore, the inventors of the present invention synthesized a series of compounds and studied their anti-inflammatory activities. As a result, they found that a compound which has pyridyl group at 6-position of pyrimidine structure and amino group, an alkoxy group, or an alkylthio group at 2- and 4-position of pyrimidine structure has excellent anti-inflammatory activity. At the same time, they successfully obtained a key intermediate (I) for producing the above compound

which is useful as a medicament, and attained the present invention.

Method of the present invention is presented as shown in the following reaction formula:



wherein R^2 represents a lower alkyl group, X represents a halogen atom, and R^1 has the same meaning as above.

The present invention thus relates to a method of producing 4-hydroxy-6-pyridylpyrimidine, by preparing Compound (IV) by allowing a lower alkyl ester of pyridinoyl acetic acid (II) to react with thiourea (III), and by subsequently treating Compound (IV) with halogenated alkyl (V).

The following will explain the present invention in further detail.

Compound (II), which is used as a starting material of the method of the present invention, may be any of 2-, 3-, and 4-position-substituted compounds. R^2 is preferably a lower alkyl group having 1 to 4 carbon atoms. The material compound (V) may be a halogenated alkyl that can alkylate the mercapto group of the intermediate (IV). As X, iodine atom, bromine atom, or the like is preferable. As R^1, a lower alkyl group having 1 to 4 carbon atoms is preferable.

In the method of the present invention, the compound of formula (IV) is first produced through the reaction of the compound of formula (II) and the compound of formula (III) in the presence or absence of a base in a solvent. As the base, an inorganic base such as an alkali metal carbonate (for example sodium carbonate and potassium carbonate), and an alkali metal hydroxide (for example sodium hydroxide and potassium hydroxide), or an organic base such as a metal alcoholate (for example sodium methylate and sodium ethylate), an alkali metal amide, a tertiary amine, a quaternary ammonium salt, or the like may be used. A metal alcoholate is generally preferable.

As the solvent, a lower alcohol such as methanol, ethanol, or n-propanol, a hydrocarbon such as benzene, toluene, or xylene, an ether such as ether, methyl ethyl

ether, dioxane, tetrahydrofuran, an ketone such as acetone or methyl ethyl ketone, methyl cellosolve, dimethylsulfoxide, or dimethylformamide may be used.

Alcohol such as methanol or ethanol is generally preferable. The reaction completes after 10 to 50 hours at from room temperature to 150℃. The reaction is preferably conducted at around the boiling point of the solvent for about 30 hours.

The reaction of the compound of formula (IV) and the compound of formula (V) is conducted in a manner similar to that of the condensation reaction step of the compound of formula (II) and the compound of formula (III) as describes above, and the base and solvent similar to those used in the above reaction are used. The reaction is conducted at 0 to 80℃ for 1 to10 hours, preferably at room temperature for about three hours.

As described above, the compound of formula (I), which can be prepared by the method of the present invention, is a novel compound that was synthesized by the inventors of the present invention for the first time, and is useful as a synthetic intermediate of a compound having anti-inflammatory activity.

The above compound having anti-inflammatory activity can be prepared for example by oxidizing and halogenating 2- and 4- position of Compound (I), respectively, to afford 2-sulfoalkyl-4-halogeno compound, and by treating the compound with an amine, alcohol, thioalcohol, or the like.

Examples

Preparation of 2-mercapto-4-hydroxy-6-(4-pyridyl)-pyrimidine (IV):

Metal sodium (23 g) is dissolved in ethanol (500 ml). The solution is added with thiourea (38 g) and isonicotinoyl acetic acid ethyl ester (89.5 g), and refluxed over night. After the reaction is completed, the solvent is evaporated. The residue was added with water and 10 % aqueous sodium hydroxide to be dissolved, and the solution is filtered. The filtrate is added with acetic acid to achieve pH 6, and precipitated crystals are separated with filtration. The crystals are washed with ethanol and dried to obtain 50.7 g (yield 53.4 %) of compound (IV) that has melting point of 300℃ or more.

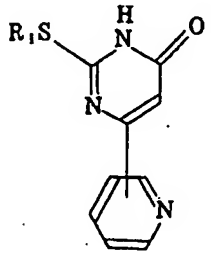
Preparation of 2-methylthio-4-hydroxy-6-(4-pyridyl)-pyrimidine (I):

Compound (IV) (205 mg) obtained as above is dissolved in a mixture solution of aqueous 2N-sodium hydroxide solution (5 ml) and ethanol (0.5 ml). The solution is added dropwise with methyl iodide (173 mg) dissolved in ethanol (5 ml) under stirring at room temperature. After the addition is completed, the solution is stirred at the

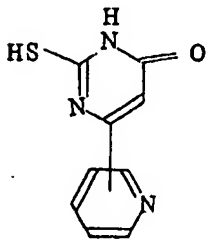
same temperature for 2.5 hours, and adjusted to pH 6 with acetic acid. The precipitates is separated with filtration and washed with water and dried to obtain 208 g (yield 95 %) of the desired compound (I) that has melting point of 300℃ or more.

Claims

1. A method of preparing a 4-hydroxy-6-pyridyl-pyrimidine derivative represented by the general formula:



wherein R^1 represents a lower alkyl group,
which is characterized in that a compound represented by formula:

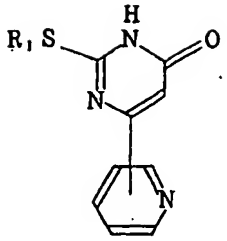


is allowed to react with a compound represented by general formula:

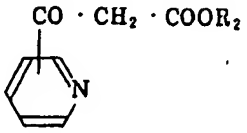
R^1-X

wherein R^1 represents a lower alkyl group and X represents a halogen atom.

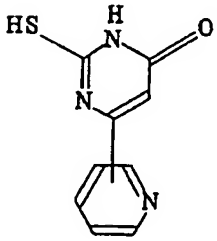
2. A method of preparing a 4-hydroxy-6-pyridyl-pyrimidine derivative represented by the general formula:



wherein R^1 represents a lower alkyl group,
which is characterized in that a compound represented by general formula:



wherein R^2 represents a lower alkyl group,
is allowed to react with thiourea to obtain a compound represented by formula:



which is then allowed to react with a compound represented by general formula:

R^1-X

wherein R^1 represents a lower alkyl group and X represents a halogen atom.